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(57) Abstract

Pharmaceutical formulations, adapted for preparing solid oral dosage forms (tablets, capsules, lozenges, etc.) having a regular and sustained release after administration. Said formulations comprise one or more active substances and a retarding base or matrix consisting of a polysaccharide of natural origin, alone or mixed with one or more natural or synthetic polymers which may be used to modify the release pattern so as to obtain a therapeutically effective formulation.

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"FORMULATION FOR PREPARING SUSTAINED RELEASE DRUGS FOR ORAL ADMINISTRATION"

The present invention relates to pharmaceutical formulations adapted to prepare solid oral dosage forms, such as capsules, tablets, lozenges and the like, having a regular and sustained release after administration.

The advantages of the sustained release or retard drugs are well known since a long time, because delaying the dissolution of the active substance, the absorption time in the gastrointestinal tract is extended, thus prolonging the therapeutic effect, at the same time avoiding or at least reducing the side effects.

For this purpose a retard formulation has to meet some criteria, namely causing a uniform and constant dissolution and being effective for an extended period of time. It is also important that such a formulation be simple to be made, the manufacturing process be reproducible and may be used for a high number of different substances.

There are several known methods for preparing retard products in the form of solid oral dosage such as tablets or capsules. Among these methods, delaying hydrophilic matrices are often used because the manufacture of finished form is simple and reproducible, it is possible to obtain a gradual and continuous release, they can be applied to many drugs and are economically advantageous.

Hydrophilic matrix is defined a homogeneous mixture of substances, substantially comprising polymers which are slowly dissolved in water and then receiving a well defined form by compression or encapsulation. When the tablet is contacted with water or aqueous based dissolution media as the gastro-intestinal juices, the hydrophilic polymers give rise to the formation of a gelatinous surface layer, through which water slowly penetrates inside, hydrating and swelling the polymer; then the polymer in the gel form, gradually goes in solution, first the outermost layer and thereafter the inner layers until it is totally dissolved and disappears.

In this way the active substance is totally and slowly released by two contemporaneous mechanisms, namely diffusion through the gelatinous layer and gel erosion.

While the first of these release mechanisms prevails in case of drugs very solubnle in the dissolution medium, the second prevails in case of poorly soluble drugs.

The polymers suitable for the preparation of hydrophilic retard matrices are relatively few, but there are already patents and publications on this subject matter.

U.S. patents N° 4,259,341 to Lowey, N°3,870,790 to Lowey et al, N°4,226,849 to Schor and N° 4,357,469 to Schor relate to the preparation of tablets

with a hydrophilic matrix comprising hydroxypropylmethylcellulose, alone or mixed with other cellulose derivatives, having undergone particular treatment such as high drying, humidification, hydrolysis, oxidation.

Also U.S. patents Nos. 4,369,172 and 4,389,393 to Schor et al relate to the use of one or more types and well defined quantities of hydroxypropylmethylcellulose alone or mixed with methylcellulose and/or sodium carboxymethylcellulose.

U.S. patents Nos. 4,167,448 and 4,126,672 to Sheth et al relate to the use of hydroxypropylmethylcellulose for preparing tablets and more particularly capsules with hydrophilic matrix having such a composition that they remain floating in the gastric juices.

The article titled "A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms by D.A. Alderman, published on Int. Journal Pharm. Techn. & Prod. Mfr. 5(3) 1-9, 1984, widely deals with the use of hydroxypropylmethylcellulose for preparing retard hydrophilic matrices and studies the influence on the drug release, of several parameters characteristic of hydroxypropylmethylcellulose such as molecular weight, substitution degree, grain size distribution, velocity of hydration.

The present invention relates to the use of hydrophilic polymers of natural origin, more particularly polysaccharides as main constituents of formulations adapted to prepare hydrophilic retard matrices for the administration of drugs in the form of tablets, lozenges, capsules and so on. Among the polysaccharides of natural origin, modified corn starch, modified corn flour and xanthan gum are preferred. The main feature of this invention consists indeed in using polysaccharides of natural origin to obtain retard matrices, this object having been

attained up to now only using hydroxypropylmethylcellulose as single or main hydrophilic polymer. In the relevant literature moreover these polysaccharides of natural origin are generally used in water solution as thickeners to stabilize emulsions, suspensions, creams, latices and the like, and their use as basic excipients for preparing solid matrices is never cited.

According to the present invention it was indeed found that use of polysaccharides of natural origin allows to obtain matrices giving rise to a sustained and gradual drug release; moreover by varying the quantity of the polysaccharide of natural origin in the formulation according to the solubility and dosage of the drug, it is possible to change the pattern of in vitro drug release. As a matter of fact polysaccharides of natural origin, which are hydrophilic polymers of high molecular weight, when they are contacted by water or gastrointestinal juices, give rapid rise to the formulation of a gelatinous surface layer controlling the further diffusion of water or gastrointestinal juices to the interior and consequently the drug release.

Water or juices penetrate inside the matrix in subsequent layers gradually transforming the polymer into a gelatinous mass and then dissolving it while active substance is at the same time released.

Another advantage of polysaccharides of natural origin is that they allow to extend release of a great number of drugs, irrespective of their dosage and solubility, by employing economical and reproducible manufacturing processes.

Still another advantage is given by the possibility of preparing formulations giving rise to retard matrices releasing the drug even in very long times that may even reach 24 hours so as to allow only one single administration per day.

Xanthan gum is a high molecular natural carbohydrate and more particularly an exocellular biopolysaccharide produced by a fermentation process of the

microorganism Xanthomonas campestris. Structure, molecular weight and properties of dissolution of this natural polymer are constant and reproducible under strictly controlled operative conditions. Xanthan gum, know also under the registered names of Keltron R and Kelzan R, is used in many fields, such as the food, drug and cosmetic field. In these cases the thickening and stabilizing property of emulsions or suspensions given by xanthan gum in solution is used. Precooked modified corn starch known under the trademark Instant Cleargel R is used, like generally all starches, as a thickening, binding, stabilizing or gelling agent, especially in the food industry, for instance as a thickener for instance of deeply frozen desserts, mayonnaise and sauces in general.

In the following description only xanthan gum is generally mentioned, but the same arguments obviously apply also in case of Instant Cleargel R, of other starches and modified flours and generally of all hydrophilic polysaccharides of natural origin.

With the present invention it was found that it is possible to utilize the properties of xanthan gum even for solid formulations of drugs, using it for preparing hydrophilic matrices in which xanthan gum has the effect of delaying the drug dissolution.

Matrix may comprise either xanthan gum alone or a mixture of xanthan gum with other natural or synthetic polymers, having the effect of varying the drug release curve so as to obtain those more adapted to reach the maximum in vivo bioavailability and efficiency thereof.

Therefore it is posssible to mix to xanthan gum the following:

1) polymers hydrating and dissolving in water such as methylcellulose, hydroxy-ethylcellulose, gum arabic, polyvinylpyrrolidone, gelatine;

2) polymers having a pH dependent solubility such as shellac, cellulose acetophtalate, xydroxypropylmethylcellulose phtalate, polyvinylacetophtalate, polyacrylates;

3) polymers hydrating and dissolving slowly in water, such as xydroxypropylmethylcellulose, modified starch and rubber of natural origin.

Matrix is therefore comprising xanthan gum, in a percentage varying between 31 and 100% and preferably between 50 and 100%, alone or mixed with one or more polymers of one or more of the three above mentioned groups, in a quantity between 0 and 69% and preferably between 0 and 50% .

The retarding matrix is mixed in a suitable apparatus with the drug or even more drugs, which are intended to be administrated in a sustained release form. Among the possible drugs, the following are cited as illustrative non limiting examples only:

adrenergic amines (ethylephrine, phenylephrine, phenylpropanolamine, d-pseudoephedrine), antispasmodics (scopolamine and other belladonna alkaloids, papaverine and its derivatives), antihistaminics (bronchopheniramine, chloropheniramine, diphenylpyraline, dimenhydrinate), anorexics (norpseudoephedrine, phenermine, diethylpropione, phenfluramine), antiasthmatics (theophylline, sulbutamol, terbutaline), antianginics (isosorbide - 5 - mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, nitroglycerin, nifedipine, dilthiazem), antiflammatories and antipyretics (indomethacine, ibuprofen, ketoprofen, acetylsalicylic acid, paracetamol, phenacetine), hypotensives (nifedipine, hydrolazine, prazosine, verapamil), antidepressants (anitryptiline, lithium salt), antitussives (dextromethorphan , noscapine, codeine), gastroenterics (cimetidine, ranitidine, methoclopramide), antiarrhythmics (procainamide, lidocaine, flecainide, propophenone),

analgesics (morphine), vitamins (ascorbic acid) and their salts used in the pharmaceutical field.

In addition to polymers and drugs, in the formulation there may be also inert excipients commonly used by men skilled in the art to improve the characteristics of said formulation.

Thus for instance, lubricants, dyestuffs, sweeteners, flavouring agents, inert excipients and so forth may be added in the preparation of tablets in order to improve flowance of powders, appearance, taste, dosage precision and the like.

The quantity of matrix used to delay drug release may therefore be varied in a broad interval, depending whether the formulation comprises only drug and matrix or other excipients are present in a more or less high amount according to the high or low level of solubility and/or the high or low dosage of the active substance.

Therefore said matrix may vary between 10 and 80% by weight of the formulation and preferably between 20 and 60% by weight.

The following examples are intended to better clarify the invention and it is to be understood that they are not limiting the scope of the invention, as many variations may be readily apparent to a man skilled in the art.

EXAMPLE 1 - 3

Sustained release tablets of theophylline (dosage 350 mg) were prepared, containing the percentages of delaying substances set forth in the following table:

Example N°	Xanthan gum %	Hydroxypropylcellulose %
1	27.2	9.0
2	19.8	9.9
3	10.1	10.1

Tablets of 350 mg each were prepared with the following excipients:

Ingredients	Example 1		Example 2		Example 3	
	g	mg/tablet	g	mg/tablet	g	mg/tablet
1) Theophylline	105.0	350.0	105.0	350.0	105.0	350.0
2) Xanthan gum	45.0	150.0	30.0	100.0	15.0	50.0
3) Hydroxypropyl-cellulose	15.0	50.0	15.0	50.0	15.0	50.0
4) Flame silica	0.6	2.0	0.6	2.0	0.6	2.0
5) Magnesium stearate	0.8	3.0	0.9	3.0	0.9	3.0

The ingredients 1, 2 and 3 were mixed for 15 minutes. Then ingredient 4 was added and after further 15 minutes of mixing, also the ingredient 5 was added. The mixture was agitated for 10 minutes and then subjected to compression in a tabletting machine with punches of 15 x 6 mm (r = 5.0 mm) to make about 250 candle shaped tablets with double fracture line.

Samples were obtained having the following characteristics:

Sample	Average weight mg/tablet	Thickness mm	Harness Kg	Friability 10 x 4 %
1	555	5.88	13.1	0.26
2	505	5.33	13.4	0.20
3	455	4.85	13.7	0.22

Hardness of the tablets was determined with the apparatus Erweka TBH 28 and friability with the apparatus Roche Friabilator at 25 rpm checking the loss of weight of 10 tablets after 4 minutes of rotation.

In vitro release of the tablets was determined with the rotary blade method described in USP, XXI ed., page 1244, employing according to the kind of analysis, the proper vessels containing 500 ml of artificial gastric juice (pH 1.2) or 500 ml of artifical intestinal juice (pH 6.8) preheated at 37° C. The vessels were closed and agitator was regulated at a speed of 150 rpm. In each vessel a tablet corresponding to 350 mg of active substance was added.

At predetermined intervals of 1, 2 , 4, 8, 12 and 14 hours a sample of 5 ml was taken and the vessel refilled with the same amount of juice or fluid. The sample was suitably diluted and analyzed at the spectrophotometer at a wavelength of 270 nm in 100 N HCl against standard reference.

The results of the analysis, given in the following table, show that the release of theophylline occurs in 12 or more hours according to the matrix composition.

Sample	Buffer pH	Cumulative release %					
		1h	2h	4h	8h	12h	14h
1	1.2	10.5	17.0	27.2	40.7	51.9	58.2
	6.8	7.8	12.8	22.4	47.8		
2	1.2	11.8	18.8	30.3	49.8	61.4	66.3
	6.8	9.1	15.7	24.9	48.1		
3	1.2	17.2	25.6	39.7	71.4	93.8	100.0
	6.8	15.6	25.6	42.5	70.6		

EXAMPLES 4-5

Theophylline tablets (dosage 350 mg) were prepared, in which the delaying substances are present in the amount given below:

Example N°	Xanthan gum %	Hydroxypropyl-methylcellulose %	Hydroxypropyl-cellulose %
4	11.0	5.5	5.5
5	10.9	10.9	----

Tablets of 350 mg each were prepared with the following excipients:

Excipients	Example 4		Example 5	
	g	mg/tablet	g	mg/tablet
Theophylline	105.0	350.0	105.0	350.0
1) Xanthan gum	15.0	50.0	15.0	50.0
2) Hydroxypropyl-cellulose	7.5	25.0	15.0	50.0
3) Hydroxypropyl methylcellulose	7.5	25.0	--	--
4) Flame silica	0.6	2.0	0.6	2.0
5) Magnesium stearate	1.5	3.0	1.5	5.0

Mixing was effected in the manner described in Examples 1-3. The mixture was subjected to compression in a tabletting machine with punches 15 x 6 mm (r = 5 mm) to make about 250 candle-shaped tablets with double fracture line. The samples had the following characteristics:

Sample N°	Average Weight mg/tablet	Thickness mm	Hardness Kg	Friability %
4	457	4.87	13.4	0.1
5	457	4.85	13.7	0.1

Hardness and friability of the tablets were measured with the apparatus described in Examples 1-3.

In order to check the in vitro release, the same method used for Example 1-3 was employed and the results given in the following table were found, from which one can see the delayed release of the drug due to the xanthan gum based matrix.

Sample N°	Buffer pH	Cumulative release %					
		1h	2h	4h	8h	12h	14h
4	1.2	17.8	29.0	47.4	80.2	95.9	
	6.8	12.6	23.2	38.7	58.8	79.7	
5	1.2	15.3	25.1	40.5	65.5	88.7	100
	6.8	12.3	21.0	34.2	55.1	81.4	100

EXAMPLE 6

Theophylline tablets (dosage 350 mg) were prepared, containing as delaying substance 22% xanthan gum. The tablets had the following composition:

Ingredients	Example 6	
	g	mg/tablet
Theophylline	105.0	350.0
Xanthan gum	30.0	100.0
Flame silica	0.6	2.0
Magnesium stearate	0.9	3.0

Mixing was effected as in Examples 1-3. Mixture was subjected to compression in a tabletting machine with punches 15 x 6 mm (r = 5 mm) to make about 250

candle shaped tablets with double fracture line having the following characteristics:

Sample N°	Average weight mg/tablet	Thickness mm	Hardness Kg	Friability %
6	455	4.85	13.76	0.2

and the following in vitro release:

Sample N°	Buffer pH	Cumulative release %					
		1h	2h	4h	8h	12h	14h
6	1.2	12.5	20.2	31.2	45.9	58.1	63.8
	6.8	7.6	13.8	25.4	45.9	88.9	100.0

EXAMPLE 7

Tablets of 50 mg of amitryptiline retard were prepared containing 16.6% of xanthan gum and 16.6 % of hydroxypropylcellulose, as costituents of the delaying matrix.

The tablets of 50 mg were prepared with the following excipients:

Ingredients	Example 7	
	g	mg/tablet
Amitryptiline	25	50.0
Xanthan gum	10	20.0
Hydroxypropylcellulose	10	20.0
Lactose	13.75	27.5
Flame Silica	0.25	0.5
Magnesium stearate	1.00	2.0

Mixing was effected as in Examples 1-3. The mixture was subjected to compression in a tabletting machine with punches 4 x 9 mm to make about 350 flat candle tablets. The samples had the following characteristics:

Sample N°	Average weight mg/tablet	Hardness Kg	Frability %
7	120	7.06	0.1

Hardness and friability of the tablets were measured with the apparatus described in Examples 1-3.

In order to check the in vitro release the same method used in Examples 1-3 was employed and the following results were obtained:

Sample N°	Buffer pH	Cumulative release %					
		1h	2h	4h	8h	12h	14h
7	12.2	33.3	48.8	72.8	100		

EXAMPLES 8-9

Retard tablets of methoclopramide chlorohydrate were prepared with a dosage of 30 mg of methoclopramide, containing either 29.2 % xanthan gum, 14.6% hydroxypropylcellulose and 14.6 % hydroxypropylmethylcellulose (Ex. 8) or 31.9% xanthan gum and 31.9% hydroxypropylmethylcellulose (Ex. 9) as constituents of the delaying matrix. The tablets of 30 mg methoclopramide were prepared with the following excipients:

Excipients	Example 8		Example 9	
	g	mg/tablet	g	mg/tablet
Methoclopramide HCl	16.8	33.7	16.8	33.7
Xanthan gum	17.5	35.0	17.5	35.0
Hydroxypropyl-cellulose	8.7	17.5		
Hydroxypropylmethyl-cellulose	8.7	17.5	17.5	35.0
Spray Dry Lactose	5.1	10.3		
Flame silica	1.0	2.0	1.0	2.0
Magnesium Stearate	2.0	4.0	2.0	4.0

Mixing was effected in the same manner as in Examples 1-3. The mixture was subjected to compression in a tabletting machine with punches 4 x 9 mm to make about 500 flat candle tablets having the following characteristics:

Sample N°	Average weight mg/tablet	Hardness Kg	Friability %
8	123	9.8	0.2
9	114	11.6	0.2

Hardness and friability of the tablets were measured with the apparatus described in Examples 1-3. In order to check the in vitro release the same method of Examples 1-3 was used with the only change that the agitator was set at a speed of 125 rpm instead of 150 rpm.

The methoclopramide tablets had the following in vitro release:

Sample	Buffer pH	Cumulative release %					
		1h	2h	4h	8h	12h	16h
8	1.2	41.2	59.5	82.8	96.3	100.0	
	6.8	35.2	49.1	68.7	82.0	91.3	97.6
9	1.2	34.1	49.9	71.6	94.0	100.0	
	6.8	28.6	41.8	60.7	82.9	94.1	99.2

Retard tablets of methoclopramide chlorohydrate of 30 mg methoclopramide were prepared, containing 58.6 % xanthan gum as a delaying substance. The 30 mg methoclopramide tablets were prepared with the following excipients:

Ingredients	Esempio 10	
	g	mg/tablet
Methoclopramide HCl	16.8	33.7
Xanthan gum	35.1	70.3
Spray Dry Lactose	5.0	10.0
Flame silica	1.0	2.0
Magnesium stearate	2.0	4.0

Mixing was effected in the same manner as in Examples 1-3. The mixture was subjected to compression in a tabletting machine with punches 4 x 9 mm to make about 500 flat candle tablets having the following characteristics:

Sample N°	Average weight mg/tablet	Hardness Kg	Friability %
10	126.4	7.7	0.2

Hardness and friability of the tablets were measured with the apparatus described in Examples 1-3. In order to check the in vitro release the same method used for Examples 8 and 9 was employed. The tablets had the following in vitro release:

Sample N°	Buffer pH	Cumulative release %					
		1h	2h	4h	8h	12h	16h
10	1.2	43.8	61.5	84.0	100		
	6.8	27.8	41.8	61.6	85.4	93.5	98.6

EXAMPLES 11-13

Retard tablets of theophylline with a dosage of 350 mg were prepared, containing the percentages of delaying substances indicated in the following table:

Example N°	Instant Cleargel R %	Hydroxypropylcellulose %
11	26.9	9.0
12	19.7	9.0
13	10.9	10.9

The tablets of 350 mg were prepared with the following excipients:

Ingredients	Example 11		Example 12		Example 13	
	g	mg/tablet	g	mg/tablet	g	mg/tablet
Theophylline	105	350	105	350	105	350
Instant Cleargel	45	150	30	100	15	50
Hydroxypropyl-cellulose LF	15	50	15	50	--	--
Hydroxypropyl-cellulose HF	--	--	--	--	15	50
Flame silica	0.6	2	0.6	2	0.6	2
Magnesium stearate	1.5	5	1.5	5	1.5	5

was compressed in a tabletting machine with punches 15 x 6 mm (r = 5 mm) to make about 250 candle shaped tablets with double fracture line. The samples had the following characteristics:

Sample N°	Average weight mg/tablet	Thickness mm	Hardness Kg	Friability %
11	557	5.00	13.1	0.1
12	507	5.56	13.7	0.1
13	457	5.12	15.6	0.1

Hardness and friability of the tablets were measured with the apparatus described in Examples 1-3.

In order to check the in vitro release the same method used for Examples 1-3 was employed and the results are given in the following table, where one can see

the delaying effect of drug release due to the matrix based on Instant Cleargel R:

Sample N°	Buffer pH	Cumulative release %					
		1h	2h	4h	8h	12h	14h
11	1.2	20.2	38.1	60.3	81.2		
12	1.2	28.3	45.1	68.5	88.1		
13	1.2	28.1	35.4	48.7	71.9	87.0	93.5
	6.8	31.2	37.9	49.6	70.0	84.7	91.5

EXAMPLE 14

Theophylline tablets with a dosage of 350 mg were prepared, containing as delaying substance 22% of Instant Cleargel R. The tablets had the following composition:

Ingredients	Example 14	
	g	mg/tablet
Theophylline	105	350
Instant Cleargel	30	100
Flame silica	0.6	2
Magnesium Stearate	1.5	5

Mixing was effected as in Examples 1-3. The mixture was subjected to compression in a tabletting machine with punches 15 x 6 mm (r = 5 mm) to make about 250 candle-shaped tablets with double fracture line having the following characteristics:

Sample N°	Average weight mg/tablet	Thickness mm	Hardness Kg	Friability %
14	457	5.00	14.1	0.1

and the following in vitro release:

Sample N°	Buffer pH	Cumulative release %			
		1h	2h	4h	8h
14	1.2	28.1	35.4	48.7	71.9

EXAMPLE 15

Hard gelatin capsule (size 1, transparent neutral colour) of theophylline (dosage 100 mg) were prepared, containing as delaying substance 33.3 % of xanthan gum with the following composition:

Ingredients	Example 15	
	g	mg/tablet
Theophylline	30	100
Xanthan gum	60	200

The mixture was prepared as in the Examples 1-3.

The capsules were filled with a laboratory capsule filling machine of the Zuma type in order to make 300 capsules.

For controlling the in vitro release the same method used for Examples 1-3 was employed, with the only variant that the agitator was set at a speed of 75 rpm instead 150 rpm.

The theophylline release from the capsules is delayed by the Xanthan gum matrix as shown by the following values of in vitro release:

Sample N°	Buffer pH	Cumulative release %			
		1h	2h	4h	8h
15	1.2	21.2	36.3	60.1	83.0

It is therefore clear, from the foregoing description and the illustrative examples, that the desired objects are fully attained, while it is also to be understood that many variations, modifications, additions and/or substitutions of elements may be resorted to the formulations according to the present invention, without departing however from its spirit and objects and without falling outside its scope of protection, as it is defined in the appended claims.

CLAIMS

1. Formulation for preparing solid dosage forms having a regular and sustained release, characterized by the fact of comprising one or more active substances and a matrix, imparting the retard effect, consisting of polysaccharides of natural origin.

2. Formulation according to Claim 1, wherein the natural polysaccharide is xanthan gum.

3. Formulation for preparing solid dosage forms having a regular and sustained release, characterized by the fact of comprising one or more active substances and a matrix, imparting the retard effect, consisting of xanthan gum and one or more natural or synthetic polymers, hydrating and dissolving slowly and/or quickly in water or in the gastrointestinal juices or the dissolution velocity of which is a function of the pH value of the medium.

4. Formulation according to Claim 3, characterized in that the percentage by weight of the matrix components is preferably 50-100% of xanthan gum and 0-50% of one or more of said polymers.

5. Formulation according to Claim 3, characterized in that the matrix comprises, in addition to xanthan gum, hydroxypropylcellulose or hydroxypropyl-methylcellulose or mixtures thereof.

6. Formulation according to Claims 2, 3, 4 or 5 wherein precooked modified corn starch (Instant Cleargel ^{R}) is used instead of xanthan gum.

7. Formulation according to one or more of the preceding claims, when used for the preparation of sustained release pharmaceutical solid dosage forms, such as tablets, capsules, lozenges and the like.

8. Formulation according to one or more of the preceding claims wherein, in

addition to one or more active substances and the constituents of the delaying matrix, there are inert excipient used for obtaining the desired dosage form, such as lubricants, dyestuffs, diluents, sweeteners, flavouring agents.

9. Formulation according to one or more of the preceding claims, characterized in that the matrix has such as composition as to prolong the drug release up to 24 hours so as to allow one single administration per day.

10. Formulations for preparing sustained release drugs adapted for oral administration, substantially as hereinbefore described and as illustrated in the annexed examples, for the above mentioned objects.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 87/00124

I. CLASSIFICATI N OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/22

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	FR, A, 2143059 (MERCK PATENT) 2 February 1973 see the whole document	1,7,8,10
X	GB, A, 2055577 (AMERICAN HOME PRODUCTS) 11 March 1981 see page 1, lines 5-116; page 3, examples 1A,D,E; claims 1,9,10	1-5,7-10
X	BE, A, 901111 (BENFAR) 15 March 1985 see page 2, line 19 - end	1-4,7-10
A	EP, A, 0146863 (BAYER AG) 3 July 1985 see the whole document	6
P,X	EP, A, 0180364 (RECKITT & COLMAN PRODUCTS) 7 May 1986 see the whole document	1-4,7,8,10

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26th June 1987	28 JUL 1987
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: M. VAN MOL

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 87/00124 (SA 16814)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/07/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2143059	02/02/73	DE-A- 2130545	21/12/72
		GB-A- 1318169	23/05/73
GB-A- 2055577	11/03/81	US-A- 4248858	03/02/81
		US-A- 4309405	05/01/82
		CA-A- 1147649	07/06/83
BE-A- 901111	15/03/85	EP-A- 0182772	28/05/86
EP-A- 0146863	03/07/85	AU-A- 3658984	27/06/85
		DE-A- 3346571	04/07/85
		JP-A- 60152411	10/08/85
		US-A- 4601895	22/07/86
EP-A- 0180364	07/05/86	GB-A- 2165451	16/04/86
		AU-A- 4873385	24/04/86
		JP-A- 61112019	30/05/86